

DAIDS	Appendix 5	No.: DWD-POL-SR-01.00A5
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DAIDS SAFETY MONITORING COMMITTEE (SMC) GUIDELINES

1. ROLES AND RESPONSIBILITIES

A Safety Monitoring Committee (SMC) is an independent group of experts that advises NIAID and the study investigators for some Phase I and most Phase II trials. Most Phase I trials may be monitored by the study team, usually working with an Independent Safety Monitor (ISM). Some large/long term Phase II trials may be monitored by a DSMB instead of an SMC. All Phase III/IV trials will be monitored by a DSMB.

The primary responsibility of the SMC is to monitor participant safety. The SMC considers study-specific data as well as relevant background information about the disease, study agent, and target population under study. The contents and schedule of reports to be reviewed by the SMC will be specified in the Study Data Monitoring Plan (SDMP) with input from the SMC. A member of an SMC may be designated to serve as an ISM and review selected individual case adverse event reports and/or periodic cumulative adverse event reports in addition to those reviewed by the entire SMC.

Prior to the first data review and preferably prior to study initiation, the SMC should define its deliberative processes. These may include event triggers that would call for an unscheduled review, guidelines for stopping administration of study product and accrual or unmasking (unblinding), and voting procedures. The SMC is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

The SMC should review the protocol and the SDMP, and identify any major concerns prior to implementation. During the trial the SMC should review:

- Study progress and safety data
- Adherence to the protocol
- Factors that might affect the study outcome or feasibility or compromise the trial data (such as slow accrual, poor data quality or timeliness, protocol violations, losses to follow-up, etc.)
- Data relevant to proceeding to the next stage of the study, if applicable
- If appropriate, effectiveness outcomes/endpoints

Other relevant issues, such as endpoint evaluability, pharmacokinetics and/or immunogenicity data, site performance, and factors external to the study may also need to be considered.

The SMC should conclude each review with the committee's recommendation to NIAID as to whether the study should continue, be modified, or be terminated. Recommendations

regarding modification of the design and conduct of the study may include corrective actions when performance is unsatisfactory, or recommendations to advance to the next dose in a dose escalation study, for example, or to the next stage in product testing.

Confidentiality must always be maintained during all phases of SMC review and deliberations. Only members of the SMC and the study biostatistician should have access to the emerging study data sorted by treatment group (even if the group identities are masked). Exceptions may be made when the SMC deems it appropriate. Whenever masked data are presented to the SMC, the key to the group coding must be available for immediate unmasking.

2. MEMBERSHIP

The membership of the SMC should reflect the disciplines and medical specialties necessary to interpret the data from the clinical trial and to fully evaluate participant safety. The SMC generally consists of at least three voting members. Membership may include an Independent Safety Monitor (ISM) with expertise in the clinical aspects of the disease/patient population being studied, and expertise in current clinical trials conduct and methodology. An SMC may also include one or two members of a standing NIAID DSMB and this may be required by NIAID.

Strong consideration should be given to including an independent biostatistician if statistical tests of the data will be evaluated. A biostatistician, as well as other specialists, may be invited to participate as non-voting members on an ad hoc basis at any time if additional expertise is desired. SMC and ad hoc members may be from the principal investigator's institution or from other participating sites but cannot be directly involved with the trial or under the supervision of a trial investigator. Furthermore, the SMC members should generally be in a different organizational group than the Principal Investigator (PI).

NIAID and other NIH staff who are not involved in the study may also participate as voting members. However, members of the sponsoring NIAID Branch are discouraged from having voting privileges. Medical Officers/Medical Monitors or other NIH staff involved in the study may participate as ex officio, non-voting members. Representatives of the manufacturer (industrial collaborator) of the test substance(s) or any other individual with vested interests in the outcome of the study are not eligible to serve on the SMC as ad hoc, ex officio or voting members.

Conflict of Interest

SMC voting members cannot have any other involvement in the conduct of the study. Furthermore, no member may have certain financial, proprietary, professional, or other interests that could affect impartial, independent decision-making by the SMC. Letters of invitation to prospective SMC and ad hoc members should include the following: "Acceptance of this invitation to serve on the SMC for this study confirms that I do not have any financial or other interest with any of the collaborating or competing pharmaceutical firms or other organizations involved in the study that constitute a potential conflict of interest." In addition, all SMC voting and ad hoc members will sign a Conflict of Interest certification to that effect at the time they are asked to participate (see Attachment

1). At the beginning of every SMC meeting, NIAID program staff or the SMC Chair will reconfirm that no conflict of interest exists for SMC members. Interests that may create a potential conflict of interest must be disclosed to the SMC prior to any discussion. The SMC will determine how to handle such potential conflict. The SMC can require that a member with a potential conflict not vote or take other means deemed appropriate. NIAID may dismiss a member of the SMC in the event of unmanageable potential conflict.

Selection and Invitation to Participate

NIAID is primarily responsible for the formation of the SMC, unless the Clinical Terms of Award for a grant specifically identifies this as the responsibility of the grantee or this responsibility is subsequently delegated in writing by NIAID to the grantee. If the grantee is primarily responsible, the proposed roster of members, curriculum vitae (including the Chairperson) and the proposed charter and operating procedures must be submitted to the NIAID Program or Project (PO) for review at least 30 days before the projected data for study initiation. However, in some cases, SMC voting members may be asked to select the Chair.) This proposal must be approved by NIAID in writing before the trial may be initiated.

3. MEETINGS OR TELECONFERENCES

The structure and operating procedures for a SMC are usually less formal than that of a DSMB. The initial SMC meeting or teleconference should occur before the start of the trial or as soon thereafter as possible. NIAID staff will usually discuss NIAID's perspective on and expectations for the study at this time. At this session, the SMC should discuss the protocol and the suggested triggers for data review, define a quorum, and establish guidelines for monitoring the study. The SMC should decide whether any member(s) should serve as an ISM and receive individual case reports of serious adverse events and/or cumulative AE reports at specified interval between the scheduled interim SMC reviews. Guidelines for stopping the study for safety concerns should be established. At this meeting, the SMC should also develop procedures for conducting business (e.g., data required for review, voting rules, attendance, etc.). Teleconference calls are usually the most appropriate means for conducting meetings.

Based on initial discussions, the SMC should decide whether to have additional ad hoc meetings based on the occurrence of certain types or frequencies of adverse events. Scheduling of meetings should be based on the magnitude of the perceived risks, decision points in the protocol (e.g., the decision to move to a higher dose), rate of enrollment, or problems that occur during the progress of the study. The SMC may be asked for advice at the conclusion of the study about whether to proceed with the next phase of development of the study product.

NIAID is responsible for convening meetings or conference calls as needed unless this has been delegated in writing to the grantee. However, meetings may be requested for cause by any member of the SMC, the principle investigator, an IRB/EC, an industrial sponsor, or NIAID. The principle investigator will be responsible for ensuring the distribution of materials for review to SMC members and other meeting participants.

3.1 SMC Meeting Format

The recommended meeting format may consist of the following sessions: Open Session, Closed Session, and Closed Executive Session (optional).

3.1.1 Open Session

Occurrences of adverse events and toxicity issues are reviewed. Issues relating to the general conduct and progress of the study should also be considered. Efficacy outcome results must not be discussed during this session and, for comparative trials, no study group-specific data will be reviewed or discussed.

SMC members (voting and ex officio), NIAID staff members, and any ad hoc experts attend and participate in this session. The principle investigator and study statistician, if applicable, should attend and participate to present results and respond to questions. This session is open to study investigators, coordinating center staff, representatives for industrial collaborators, representatives from the Food and Drug Administration (FDA), and NIH program and regulatory staff.

3.1.2 Closed Session

Study group-specific data including all relevant efficacy outcome measures, masked if so specified, are presented at this session. This session is normally attended only by voting members, non-voting (ex officio and ad hoc) members, and the study statistician. The voting members can choose as a group to make decisions and formulate recommendations either during this session or during a Closed Executive Session.

3.1.3 Closed Executive Session (optional)

This final session involves only voting members to ensure complete independence for making decisions and formulating independent recommendations. The SMC may unmask the data during this session based on procedures identified in advance.

3.2 Voting

A quorum, as defined by the SMC in the initial meeting, must be present either in person or by teleconference. After a thorough discussion of SMC members' opinions and rationale, the final recommendations of each SMC member should be solicited in either Closed Session or Closed Executive Session. The final recommendations are recorded and either identified as majority or minority positions (if a general consensus is achieved) or followed by a vote for recommendations without an achievable consensus.

4. STUDY-RELATED INFORMATION AND REPORTS FOR SMC REVIEW

It is the responsibility of the PI to ensure that the SMC is apprised of all new safety information relevant to the study product and the study. If applicable, this includes providing the SMC with a copy of the Clinical Investigator's Brochure (CIB) in advance of the first SMC session, as well as promptly providing all IB revisions and all safety reports issued by the industrial sponsor. Summary safety and enrollment data must be forwarded periodically to the SMC as directed by the SDMP. The SMC must receive all protocol revisions and may receive other documents relating to the study, such as annual reports, manuscripts, and newsletters. Other relevant new information, e.g. results from studies of the same or similar agents or important preclinical testing results, must also be provided on a timely basis.

The SMC will review the SDMP and the proposed general content of the SMC monitoring reports at the initial meeting. The SMC may request changes or additions to the actual data elements to be presented and to the proposed review schedule. At each meeting, further additions or modifications to these reports may be directed by the SMC on a one-time or continuing basis. Distribution of written reports must allow sufficient time for review.

Reports for meetings of the SMC will consist of the Open Session Report and, as required, a Closed Session Report. Open Session reports are distributed to all SMC members, selected NIAID staff, and other appropriate persons as directed by the SMC. Closed Session reports are distributed only to SMC members and others as designated by the SMC. The Closed Session Report may contain study group-specific outcome data and should be marked confidential and handled accordingly.

5. REPORTS FROM THE SMC

5.1 Verbal Report

At the conclusion of a SMC meeting, the SMC should discuss its findings and recommendations with NIAID representatives and the study investigators. If NIAID is not represented at the meeting, the SMC Chair should contact the NIAID PO immediately after the meeting for debriefing.

5.2 Summary Report

The SMC will issue a written report summarizing topics discussed by the SMC and describing their findings, overall safety assessment, and recommendations. This generally occurs after each meeting but SMCs that meet on a very frequent basis may summarize more than one meeting in a single report. The rationale for recommendations will be included when appropriate. This report will not include confidential information. The SMC Chair or designee is responsible for preparing and distributing the report.

Unless otherwise specified, the summary report will be submitted by the SMC chair to the NIAID PO. The NIAID PO will forward the report to a designated study team representative (usually the Principal Investigator) and to other appropriate NIAID staff. The study team representative is responsible for disseminating the SMC summary report to site investigators, and any IND sponsors and industrial collaborators. Site investigators must, in

turn, submit the reports to their respective IRBs/ECs in accordance with local IRB/EC policy. If the trial is being conducted under an IND, the IND holder (usually NIAID) will forward the summary report to the FDA.

5.3 Closed Session Minutes (optional)

The SMC may also prepare confidential minutes that include details of discussions in the closed session(s). Meeting minutes are to be held in strict confidence, accessible only to voting members of the SMC until a) such time when the study is closed, b) NIAID accepts a SMC recommendation for early termination, or c) if the minutes are requested by the FDA or NIAID for patient safety or regulatory purposes.

5.4 Immediate Action Report

The SMC Chair will notify the NIAID PO of any findings of a serious and immediate nature, such as if the SMC recommends substantial study modifications or that all or part of the trial be discontinued. The PO will immediately inform appropriate Division staff, including their Branch Chief and others as determined by their Division. In addition to verbal communications, recommendations to discontinue or substantially modify the design or conduct of a study must be conveyed to NIAID in writing within one day of the SMC meeting. This written, confidential briefing may contain study group-specific and/or unmasked supporting data and should include the SMC members' rationale for its recommendations.

The SMC provides recommendations concerning continuation or major changes in study conduct to NIAID. After consultation with the investigators, all final decisions regarding these recommendations are made by NIAID.

Attachment 1

**CONFLICT OF INTEREST CERTIFICATION
FOR MEMBERS OF SAFETY MONITORING COMMITTEES (SMC)
NOTE: DO NOT USE FOR DSMB**

Confidential

SMC for the ABC Trial on XYZ

I have not been within the past 12 months a part-time, full-time, paid, or unpaid employee of or am not presently negotiating for employment with any organizations that are: (a) involved in the studies under review; (b) whose products or services will be used or tested in the studies under review, or (c) whose products or services would be directly and predictably affected by any outcome of these studies;

- I am not an officer, member, owner, trustee, director, expert advisor, or consultant, i.e., speaker, researcher, contractor, grantee or collaborator, of such organizations;
- I do not have any financial interests or assets that exceed \$10,000 in any organizations meeting the above criteria, nor do my spouse or dependent children or domestic partner;
- I do not have any intellectual, proprietary interest in any of the products being reviewed or in products in direct competition with such products; and,
- I have not been involved in any litigation regarding these organizations (e.g., plaintiff, defendant, expert witness).

PLEASE COMPLETE BELOW.

- ☐ No relevant interests or activities.
- ☐ I will disclose exception(s) to the SMC prior to any discussion so that they can be reflected in the minutes along with the SMC's determination as to how to handle such exception(s).

I will notify the NIAID Program/Project Officer promptly if a change occurs in any interests or activities during the tenure of my responsibilities.

I am aware of my responsibilities for maintaining the confidentiality of any non-public information that I receive or become aware of through this activity, and for avoiding using such information for my personal benefit, the benefit of my associates, or the benefit of organizations with which I am connected or with which I have a financial involvement.

Member's name (please print)

Signature

Date